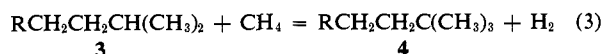


analog of the esters and neoalkanes **4** as the analogs of



the tetrahedral intermediates **2**. The assignment of tetrahedral intermediate to **B** is relatively conventional, but the formalism does not require this to be a close representation of the transition state. In this reaction it is reasonable to suppose that the transition state is not much more compressed than **B**, and that the representation should be quite good.

Free energies of formation of the necessary hydrocarbon models are available in standard tables.<sup>15</sup> Results are presented in Table I as double differences using

**Table I.** Hydrocarbon Models of Steric Effects in Ester Hydrolysis

R <sup>a</sup>	−ΔΔG <sub>298</sub> <sup>b</sup>	log <i>k</i> <sub>rel</sub> <sup>c</sup> calcd	log <i>k</i> <sub>rel</sub> <sup>d</sup> obsd
H−	(1.7) <sup>e</sup>	(1.0) <sup>e</sup>	1.24
α-Series			
CH <sub>3</sub> −	0	0	0
CH <sub>3</sub> CH <sub>2</sub> −	0.11	0.07	−0.07
(CH <sub>3</sub> ) <sub>2</sub> CH−	−0.65	−0.39	−0.47
(CH <sub>3</sub> ) <sub>3</sub> C−	−2.89	−1.72	−1.54
β-Series			
CH <sub>3</sub> CH <sub>2</sub> −	0.11	0.07	−0.07
CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> −	0.13	0.08	−0.36
(CH <sub>3</sub> ) <sub>2</sub> CHCH <sub>2</sub> −	−1.18	−0.70	−0.93
(CH <sub>3</sub> ) <sub>3</sub> CCH <sub>2</sub> −	−3.51	−2.08	−1.63

<sup>a</sup> RCOOEt, RCH(CH<sub>3</sub>)<sub>2</sub>. <sup>b</sup> From ref 15. <sup>c</sup> −ΔΔG/2.3RT with *t* = 70°. <sup>d</sup> Reference 16. <sup>e</sup> From molecular mechanics V<sub>s</sub> steric values (2(isobutane)–propane–neopentane).

ethyl acetate (isobutane to neopentane) as the reference compound. The ΔΔG values have been converted to relative rates at 70° to give calculated log *k*<sub>rel</sub> in column 3 and these are intended to reproduce the observed values in column 4,<sup>16</sup> which they do to within a factor of 2.2 out of 40, excluding the formic ester. We regard this agreement as good as can be expected until more detailed computations can be made, and it certainly is suitable for many purposes.

Several comments are in order. It turns out that roughly the same results are obtained from ΔΔ*H*<sub>298</sub> or from ΔΔ*G*<sub>400</sub>. Hence entropy effects largely cancel. Actually the free energy values pertain to the gas phase, but it is to be expected that free energies of solution will almost exactly cancel in the double difference. And finally, the reason why the tables cannot be used for formic esters is that the free energy change computed in eq 3 involves bond hybridization and other factors as well as steric factors. As long as all formal changes are identical, these other factors will largely cancel. But the model for the formic acid base converts propane to isobutane where a secondary hydrogen is replaced by methyl while in all other cases a tertiary hydrogen is replaced by methyl. We give an approximate value in parentheses based on a molecular mechanics computation using the Allinger 1971 "force field."<sup>11</sup> Since this represents a ΔΔ*H* term, it is actually not exactly comparable.

(15) D. R. Stull, E. F. Westrum, Jr., and G. C. Sinke, "The Chemical Thermodynamics of Organic Compounds," Wiley, New York, N. Y., 1969.

(16) R. W. Taft, Jr., ref 5, p 556.

**Acknowledgment.** This work was supported in part by Contract No. AF(40-1)-2690 under the Division of Biology and Medicine, U. S. Atomic Energy Commission. I am also indebted to the Computing Center at Florida State University for a grant of computer time.

DeLos F. DeTar

Department of Chemistry and Institute of Molecular Biophysics  
The Florida State University  
Tallahassee, Florida 32306

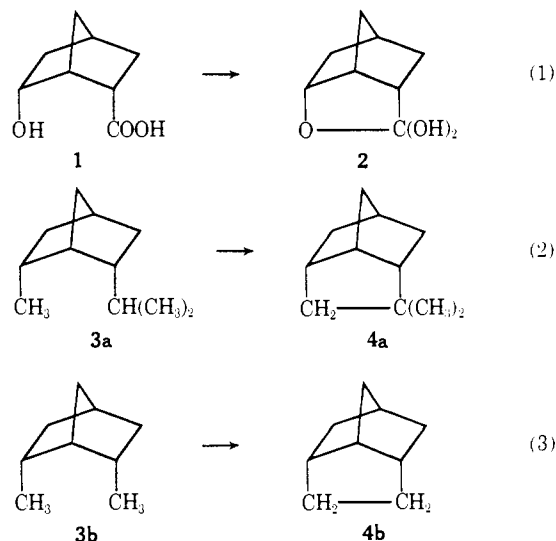
Received October 9, 1973

## Quantitative Predictions of Steric Acceleration

Sir:

We have proposed a thermodynamic formalism which serves as a guide to devising models for calculating effects of structure on reaction rates.<sup>1</sup> We have successfully used hydrocarbon models in calculating steric retardation of ester formation. This same approach gives a good account of steric accelerations in cyclizations to lactones without invoking special reaction trajectories or "orbital steering."<sup>2,3</sup> Koshland's group has provided interesting kinetic data for cyclizations covering a rate range of more than 10,000. We have computed the magnitudes of steric effects in these reactions.

In the present study we have used two hydrocarbon model systems, eq 2 and 3, for lactone formation, eq 1.



As for ester hydrolysis we have taken the tetrahedral intermediate **2** as the model for **B** in the formalism.<sup>1</sup> Hydrocarbon models **3** are used to represent the hydroxy acid **1** and hydrocarbon models **4** represent **2**. It is our hope that the steric energy difference **3a** → **4a** and **3b** → **4b** will reflect quantitatively most of the steric energy differences of **1** → **2** and that the latter will account for the observed relative rates.


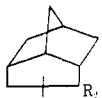
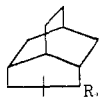
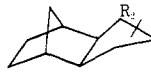
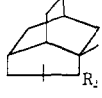
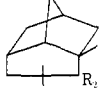
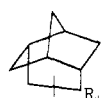
Since thermodynamic data are not available for all of the hydrocarbon models, we have calculated steric en-

(1) D. F. DeTar, *J. Amer. Chem. Soc.*, **96**, 1254 (1974).

(2) D. R. Storm and D. E. Koshland, Jr., *J. Amer. Chem. Soc.*, **94**, 5815 (1972).

(3) R. M. Moriarity and T. Adams, *J. Amer. Chem. Soc.*, **95**, 4071 (1973).

**Table I.** Steric Effects on Lactonization as Computed from Hydrocarbon Models

Compound <sup>a</sup>	$-\Delta\Delta V_s^b/1.4$		log $k_{rel}^c$
	R = H	R = CH <sub>3</sub>	
A 	0	0	0
B 	3.4 (4.4)	2.6 (3.6)	4.11
C 	-0.2 (0.3)	0 (0.5)	1.04
D 	2.9 (2.9)	2.5 (2.5)	1.92
E 	3.6 (4.1)	3.0 (3.5)	4.1
F 	6.7 (7.7)	3.7 (4.7)	<i>d</i>
G 	-1.7 (-0.2)	-6.4 (-4.9)	<i>d</i>

<sup>a</sup> Line across bond designates position of formal ring closure. For compound B, for example, see eq 1-3. <sup>b</sup> ( $V_s$  for 2,  $-V_s$  for 1)  $-\Delta V_s$  for cyclopentane for 1,1-dimethylcyclopentane). The 1.4 factor is  $2.3RT$  for 25°. The values in parentheses include a  $T\Delta S$  correction. See text. <sup>c</sup> Reference 2. <sup>d</sup> See ref 3.

ergies  $V_s$  by means of molecular mechanics.<sup>4-8</sup> The strain energy, eq 4, is defined in terms of deviations of

$$V_s = \frac{1}{2}k_{ij}(p_{ij} - p_{ij}^0)^2 + V_{nb}(r_{ki}) + \text{other terms} \quad (4)$$

bond lengths and angles,  $p_{ij}$ , from reference values,  $p_{ij}^0$ , assuming a Hooke's law function, plus terms which evaluate pairwise nonbonded energies plus other terms which evaluate Pitzer strain and certain corrections. We have used the Allinger<sup>7</sup> force field as described except for dividing torsional effects into nine parts to ensure consistency.<sup>9</sup> Results are presented in Table I.

Although the calculation is made for a static model, the method is parameterized to reflect enthalpies due to steric effects for hydrocarbons in the vapor phase at 298°K. It appears that the reliability of the double differences  $\Delta\Delta V_s$  may be of the order of 2-3 kcal/mol at the present state of development. Values have been related to  $\gamma$ -butyrolactone and its models taken as

(4) F. H. Westheimer in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N. Y., 1956, p 523.

(5) E. J. Jacob, H. B. Thompson, and L. S. Bartell, *J. Chem. Phys.*, **47**, 3736 (1967); L. S. Bartell, *J. Chem. Educ.*, **45**, 754 (1968).

(6) R. H. Boyd, *J. Chem. Phys.*, **49**, 2574 (1968).

(7) M. L. Allinger, M. T. Tribble, M. A. Miller, and D. H. Wertz, *J. Amer. Chem. Soc.*, **93**, 1637 (1971).

(8) J. E. Williams, P. J. Stang, and P. v. R. Schleyer, *Annu. Rev. Phys. Chem.*, **19**, 531 (1968).

(9) Allinger's convention uses torsion angles of 60° or less. In certain compounds this convention omits one torsion term or adds an extra. In most cases the two conventions give results which agree within about 0.5 kcal/mol or better.

0. If the model is successful, the values in columns 2 and 3 of Table I should reproduce those of column 4. The agreement is as good as can be expected for the calculated steric energies. We conclude that the approach is a useful one for predicting relatively large steric effects.

Several comments are in order. Computations based directly on the oxygen compounds 1 and 2 will certainly be in order as force fields for these compounds become more fully developed, but it will require considerable evaluation to determine whether these are more reliable than improved hydrocarbon calculations or on modifications based on hydrocarbon models. Perhaps of more importance will be evaluation of entropy changes, which can be obtained from molecular mechanics.<sup>6,10</sup> We have approximated the entropy ( $T\Delta S$ ) terms by the estimated  $\Delta G$  values in parentheses. These were based on an evaluation of the entropy changes in forming various ring compounds taken from thermodynamic data on hydrocarbons.<sup>11</sup> Cyclopentane has a relatively high entropy in comparison with *n*-pentane, while 2,6-dimethylbicyclo[2.2.1]heptane is relatively constrained in comparison with the tricyclo compound (B in Table I), and this is estimated to give a  $T\Delta S$  term of about 1.5 kcal/mol (or 1 in log  $k_{rel}$ ).

Care is needed in using CH<sub>3</sub> groups to represent oxygen atoms, for the extra hydrogen atoms may encounter steric compressions not expected for an -OR group. We therefore examined the nonbonded distances carefully for such artifacts. These are minimal for compounds A-E but are of some consequence in F. It is easy to modify hydrocarbon models to remove such artifacts should this prove advantageous.

**Acknowledgment.** It is a pleasure to acknowledge the inspiration of the work of Professor L. S. Bartell and his generosity in supplying his program for molecular mechanics computations. It is also a pleasure to acknowledge the hospitality of Professor J. Dunitz at the Eidgenossische Technische Hochschule, Zurich, which permitted me to undertake development of an expanded molecular mechanics program. Dr. Hans Buergi of ETH was a most helpful guide. This work was supported in part by Contract No. AF(40-1)-2690 under the Division of Biology and Medicine, U. S. Atomic Energy Commission. I am also indebted to the Computing Center at Florida State University for a grant of computer time.

(10) K. B. Wiberg and R. H. Boyd, *J. Amer. Chem. Soc.*, **94**, 8426 (1972).

(11) D. R. Stull, E. F. Westrum, Jr., and G. C. Sinke, "The Chemical Thermodynamics of Organic Compounds," Wiley, New York, N. Y., 1969.

DeLos F. DeTar

Department of Chemistry and Institute of Molecular Biophysics  
The Florida State University  
Tallahassee, Florida 32306

Received October 9, 1973

### Ring Construction through Transpositions of Activated Cyclopropanes

Sir:

Recently, we reported an instance of homoconjugate addition by a nucleophile disposed to execute intra-